## Sisson, Bradley

**From:** Jenkins, Kenneth E. [kejenkins@townsend.com]
**Sent:** Thursday, October 07, 2004 2:29 PM
**To:** Sisson, Bradley
**Subject:** Proposed Claim

<<ProposedClaims10-6.doc>> <<JMSpaper.pdf>>

Dear Examiner Sisson:

Thank you for your time and courteousness in the interview yesterday, October 6, 2004. As we discussed in yesterday's interview, we understand that amending the claims to recite "nuclear binding energy" would help to move this case in a positive direction.

Enclosed please find a proposed claim set. Support for the proposed amendments may be found in the specification, for example, at page 19, line 26 to page 21, line 14. A definition of the term "nuclear binding energy" may be found on page 16, lines 5-19. Support for the term "oligomeric root tag" may be found, for example, at page 58, lines 14-16.

Also enclosed for your convenience is an article that may help to clarify the unique aspects of the present invention.

Please don't hesitate to give me a call if you feel further discussion would help in moving these claims toward allowance. My direct dial is (858)350-6157.

Best regards,
Ken

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**PROPOSED CLAIM AMENDMENTS FOR EXAMINER'S REVIEW**
**APPLICATION NUMBER 10/035,349**

1. (Currently Amended) A method for sequencing a terminal portion of an oligomer, comprising:

(a) contacting said oligomer with a mass defect labeling moiety to covalently attach the mass defect labeling moiety to a terminus of the oligomer and form a labeled oligomer, said mass defect labeling moiety comprising at least one element having an atomic number from 17 to 77~~, with the proviso that said element is other than sulfur or phosphorus~~;

(b) fragmenting said labeled oligomer using an enzymatic, chemolytic or mass spectrometric fragmentation method to produce labeled oligomer fragments;

(c) identifying a mass spectrum data corresponding to said labeled oligomer fragments; and

(d) determining the sequence of at least two terminal residues of said labeled oligomer, wherein said sequence determination step **comprises discriminating between the mass of the labeled oligomer fragment and an unlabeled oligomer fragment based on the nuclear binding energy of the mass defect labeling moiety** ~~is based at least in part on the mass defect of said labeling moiety, wherein said mass defect is less than 1 amu,~~

**wherein said oligomer is selected from the group consisting of a protein, polysaccharide, nucleic acid, and lipid**.

2. (Original) The method of claim 1, wherein said labeling moiety comprises at least one element of atomic number 35 to 63.

3. (Original) The method of claim 2, wherein said labeling moiety comprises at least one element of atomic number 39 to 58.

4. (Original) The method of claim 2, wherein said labeling moiety comprises at least one element selected from the group consisting of bromine, iodine, europium and yttrium.

5. (Original) The method of claim 4, wherein said element is europium.

6. (Original) The method of claim 4, wherein said element is yttrium.

7. (Original) The method of claim 4, wherein said element is bromine.

8. (Original) The method of claim 4, wherein said element is iodine.

9. (Currently Amended) The method of claim 1, wherein said oligomer is ~~selected from the group consisting of~~ a protein~~, an oligonucleotide, an oligosaccharide and a lipid~~.

10. (Currently Amended) The method of claim ~~9~~ **1**, wherein said oligomer is ~~an oligonucleotide~~ **a polysaccharide**.

11. (Original) The method of claim 9, wherein said sequence is at least three residues.

12. (Original) The method of claim 9, wherein said sequence is at least four residues.

13. (Currently Amended) The method of claim 1, wherein several oligomers, each labeled with a different number of mass defect ~~elements~~ **labeling moieties** are mixed prior to said fragmenting or analyzing step.

14. (Currently Amended) A method for sequencing a portion of an oligomer in an oligomer mixture, said method comprising:

(a) contacting said oligomer mixture with a ~~terminus~~ **mass defect** labeling moiety to covalently attach the ~~terminus~~ **mass defect** labeling moiety to a terminus of said oligomer and form a labeled oligomer mixture, said ~~terminus~~ **mass defect** labeling moiety comprising at least one element having an atomic number from 17 to 77~~, with the proviso that said element is other than sulfur or phosphorus~~;

(b) separating individual labeled oligomers in said labeled oligomer mixture; ~~and~~

(c) identifying a mass spectrum data corresponding to said individual labeled oligomer; and

(d) analyzing said mass spectrum data to determine the sequence of at least two terminus residues of said oligomer, wherein said analysis step **comprises discriminating**

**between the mass of the labeled oligomer and an unlabeled oligomer based on the nuclear binding energy of the mass defect labeling moiety** ~~**is based at least in part on the mass defect of said labeling moiety, wherein said mass defect is less than 1 amu,**~~

**wherein said oligomer is selected from the group consisting of a protein, polysaccharide, nucleic acid, and lipid**.

**15**. (Original) A method in accordance with claim 14, wherein said element has an atomic number of from 35 to 63.

**16**. (Original) A method in accordance with claim 14, wherein said element has an atomic number of from 39 to 58.

**17**. (Original) A method in accordance with claim 14, wherein said element is selected from the group consisting of bromine, iodine, europium and yttrium.

**18**. (Original) A method in accordance with claim 14, further comprising a step prior to step (a) of isolating a group of oligomers from a biological sample.

**19**. (Original) A method in accordance with claim 18, wherein said biological sample is from a diseased tissue sample.

**20**. (Original) A method in accordance with claim 18, wherein said biological sample is from a healthy tissue sample.

**21**. (Original) A method in accordance with claim 14, wherein said separating is conducted by at least one method of capillary electrophoresis of the labeled oligomer mixture.

**22**. (Original) A method in accordance with claim 14, wherein said mass spectrometric method uses ESI-TOF MS.

**23**. (Currently Amended) A method for structure and function analysis of an oligomer having a plurality of residues, said method comprising:

(a) contacting said oligomer with a mass defect labeling reagent to differentially label exposed residues and unexposed residues and produce a differentially labeled oligomer comprising a mass defect labeling moiety, wherein said mass defect labeling reagent

comprises at least one element having an atomic number of from 17 to 77 that is other than sulfur or phosphorus;

(b) identifying a mass spectrum data corresponding to said differentially labeled oligomer; and

(c) analyzing said mass spectrum data to determine sequences of said oligomer that are exposed in the three-dimensional structure and sequences of said oligomer that are unexposed in the three-dimensional structure, wherein said analysis step **comprises discriminating between the mass of the differentially labeled oligomer and an unlabeled oligomer based on the nuclear binding energy of the mass defect labeling moiety** ~~**is based at least in part on the mass defect of said labeling moiety, wherein said mass defect is less than 1 amu,**~~

**wherein said oligomer is selected from the group consisting of a protein, polysaccharide, nucleic acid, and lipid**.

**24**. (Presently Amended) A method in accordance with claim 23, wherein said oligomer is a protein~~, a nucleic acid, or an oligosaccharide~~.

**25**. (Original) A method in accordance with claim 23, wherein said mass defect labeling reagent comprises at least one element of atomic number 35 to 63.

**26**. (Original) A method in accordance with claim ~~**26**~~ **23**, wherein said mass defect labeling reagent is bromine and said oligomer is a protein.

**27**. (Original) A method in accordance with claim 23, wherein said mass defect labeling reagent comprises at least one element of atomic number 39 to 58.

**28**. (Original) A method in accordance with claim 23, wherein said differentially labeled oligomer is fragmented by enzymatic or chemolytic methods prior to step (b).

**29**. (Original) A method in accordance with claim 23, wherein said oligomer is a protein, said mass defect is bromine or iodine and said exposed residues comprises a portion of the tyrosine residues present in said protein.

**30**. (Original) A method in accordance with claim 23, wherein said mass spectrometric method uses ESI-TOF MS.

**31**. (Original) A method in accordance with claim 29, wherein said mass spectrometric method uses ESI-TOF MS.

**32**. (Currently Amended) A method for sequencing the terminal portion of an oligomer, comprising:

(a) contacting a first sample of said oligomer with a labeling moiety to covalently attach a label to the terminus of the oligomer and form a labeled oligomer, said labeling moiety having one element with an atomic number from 17 to 77~~, with the proviso that said element is other than sulfur or phosphorus~~;

(b) contacting a second sample of said oligomer with a labeling moiety to covalently attach a label to a terminus of the oligomer and form a labeled oligomer, said labeling moiety having two elements with an atomic number from 17 to 77, ~~with the proviso that said elements are other than sulfur or phosphorus~~;

(c) optionally, repeating step (b) from one to three times with additional samples, wherein the labeling moieties have three, four or five elements, respectively, with an atomic number from 17 to 77~~, with the proviso that said elements are other than sulfur or phsophorus~~;

(d) mixing the labeled oligomers from steps (a) through (c);

(e) fragmenting said labeled oligomers using an enzymatic, chemolytic or mass spectrometric fragmentation method to produce labeled oligomer fragments;

(f) identifying a mass spectrum data corresponding to said labeled oligomer fragments; and

(g) determining the sequence of at least two terminal residues of said labeled oligomer fragments, wherein said sequence determination step **comprises discriminating between the mass of the labeled oligomer fragment and an unlabeled oligomer fragment based on the nuclear binding energy of the labeling moiety** ~~is based at least in part on the mass defect of said labeling moiety, wherein said mass defect is less than 1 amu;~~

**wherein said oligomer is selected from the group consisting of a protein, polysaccharide, nucleic acid, and lipid**.

**33**. (Original) The method of claim 32, wherein each of said elements has an atomic number of from 35 to 63.

**34**. (Original) The method of claim 32, wherein each of said elements has an atomic number of from 39 to 58.

**35**. (Original) The method of claim 32, wherein each of said elements is selected from the group consisting of bromine, iodine, europium and yttrium and said oligomer is a protein.

**36**. (Currently Amended) The method of claim 32, wherein each of said elements is selected from the group consisting of bromine, iodine, europium and yttrium and said oligomer is ~~**an oligonucleotide**~~ **a nucleic acid**.

**37**. (Currently Amended) The method of claim 32, wherein each of said elements is selected from the group consisting of bromine, iodine, europium and yttrium and said oligomer is ~~**an oligosaccharide**~~ **a polysaccharide**.

**38**. (Currently Amended) A method for sequencing a portion of an oligomer, comprising:

(a) fragmenting aliquots of said oligomer using one or more specific enzymatic or chemolytic fragmentation methods to produce oligomer fragments, wherein a different fragmentation method is applied to each aliquot;

(b) contacting a first aliquot of oligomer fragments with a first labeling moiety to covalently attach said first labeling moiety to a terminus of the oligomer fragments and form labeled oligomer fragments, said first labeling moiety having one element with an atomic number from 17 to 77~~**, with the proviso that said element is other than sulfur or phosphorus**~~;

(c) optionally contacting the other aliquots of oligomer fragments with other distinct labeling moieties to covalently attach said distinct labeling moieties to the termini of the oligomer fragments and form labeled oligomer fragments, said distinct labeling moiety having two or more elements with an atomic number from 17 to 77~~**, with the proviso that said elements are other than sulfur or phosphorus**~~;

(d) optionally mixing the aliquots of labeled oligomer fragments;

(e) identifying a mass spectrum data corresponding to said labeled oligomer fragments; and

(f) determining the sequence of at least two residues of said labeled oligomer, wherein said sequence determining step **comprises discriminating between the mass of the labeled oligomer fragments and an unlabeled oligomer fragment based on the nuclear binding energy of the labeling moiety** ~~**is based at least in part on the mass defect of said labeling moiety, wherein said mass defect is less than 1 amu,**~~

**wherein said oligomer is selected from the group consisting of a protein, polysaccharide, nucleic acid, and lipid**.

**39**. (Original) A method in accordance with claim 38, wherein said oligomer is a lipid.

**40**. (Original) A method in accordance with claim 38, wherein said oligomer is a protein.

**41**. (Original) A method in accordance with claim 38, wherein said oligomer is a nucleic acid.

**42**. (Currently Amended) A method in accordance with claim 38, wherein said oligomer is ~~**an oligosaccharide**~~ **a polysaccharide**.

**43**. (Original) A method in accordance with claim 38, wherein said elements have an atomic number of from 35 to 63.

**44**. (Original) A method in accordance with claim 43, wherein said elements have an atomic number of from 39 to 58.

**45**. (Currently Amended) A method for comparing the relative abundances of analytes from two or more samples, comprising:

(a) contacting the analytes of the first sample with a labeling moiety to covalently attach a label to the analytes and form labeled analytes, said labeling moiety having one element with an atomic number from 17 to 77~~**, with the proviso that said element is other than sulfur or phosphorus**~~;

(b) contacting the analytes of subsequent samples with labeling moieties to covalently attach labels to the analytes in each sample, wherein the labeling moieties used for each subsequent sample contain an additional element with an atomic number from 17 to 77~~; with the proviso that said elements are other than sulfur or phosphorus~~;

(c) mixing the aliquots of labeled analytes;

(d) identifying mass spectrum data corresponding to said labeled analytes; and

(e) analyzing said mass spectrum data to determine the relative abundances of one or more of the analytes between the samples, wherein said analysis step **comprises discriminating between the mass of the labeled analytes and an unlabeled analyte based on the nuclear binding energy of the labeling moiety** ~~is based at least in part on the mass defect of said labeling moiety, wherein said mass defect is less than 1 amu~~

**wherein said analyte is selected from the group consisting of a protein, polysaccharide, nucleic acid, and lipid**.

**46**. (Original) A method in accordance with claim 45, wherein said elements have an atomic number of from 35 to 63.

**47**. (Original) A method in accordance with claim 45, wherein said elements have an atomic number of from 39 to 58.

**48**. (Currently Amended) A method for tagging the elements of chemical libraries, either during synthesis or screening, comprising;

(a) contacting ~~a~~ **an oligomeric** root tag with a labeling moiety to covalently attach a label to the **oligomeric** root tag and form a labeled **tag**, said labeling moiety having one element with an atomic number from 17 to 77~~, with the proviso that said element is other than sulfur or phosphorus~~;

(b) optionally, contacting ~~a~~ **the oligomeric** root **tag** with additional labeling moieties to covalently attach additional labels to the root tag and form a multiply labeled tag, said labeling moiety having one element with an atomic number from 17 to 77~~, with the proviso that said element is other than sulfur or phosphorus~~;

(c) identifying mass spectrum data corresponding to said labeled tag; and

(d) analyzing the mass spectrum data to determine both the mass and the number of elements with an atomic number from 17 to 77 of the labeled tag, such that the mass and number of elements identifies chemical processes to which a specific chemical of the library has been exposed and the identity of the chemical from the library, wherein said analysis step **comprises discriminating between the mass of the labeled tag and an unlabeled oligomeric root tag based on the nuclear binding energy of the labeling moiety** ~~**is based at least in part on the mass defect of said labeling moiety, wherein said mass defect is less than 1 amu,**~~

**wherein said oligomeric root tag is selected from the group consisting of a protein, polysaccharide, nucleic acid, and lipid**.

**49**. (Original) A method in accordance with claim 48, wherein said elements have an atomic number of from 35 to 63.

**50**. (Original) A method in accordance with claim 48, wherein said elements have an atomic number of from 39 to 58.

**51.** (Deleted)

**52.** (Previously Presented) The method of claim 45, wherein at least a portion of said labeling moiety of step (a) is a stable isotope of said labeling moiety of step (b).

**53.** (Previously Presented) The method of claim 52, wherein said labeling moiety of step (a) and said labeling moiety of step (b) differ by 2 or more but 16 or less stable isotopes.

**54.** (Previously Presented) The method of claim 52, wherein said labeling moiety of step (a) and said labeling moiety of step (b) differ by 4 or more but 16 or less stable isotopes.

**55.** (Previously Presented) The method of claim 52, wherein said labeling moiety of step (a) and said labeling moiety of step (b) differ by 8 or more but 16 or less stable isotopes.

**56.** (Previously Presented) The method of claim 52, wherein said stable isotope is selected from the group consisting of $^{2}H$, $^{13}C$, $^{15}N$ and $^{81}Br$.

**57.** (Previously Presented) The method of claim 45, further comprising separating at least a portion of said mixture of labeled analytes prior to said analysis step (d).

**58.** (Previously Presented) The method of claim 57, wherein said separation step comprises separating at least a portion of said mixture of labeled analytes by electrophoresis, chromatography or affinity separation.